DOI:10.1111/j.1477-2574.2012.00580.x HPB

ORIGINAL ARTICLE

Incidence and predictive factors of clinically relevant bile leakage in the modern era of liver resections

Antoine Guillaud[1]*, Claire Pery[1]*, Boris Campillo[2], Anne Lourdais[2], Sulpice Laurent[1] & Karim Boudjema[1]

[1]Service de Chirurgie Hépatobiliaire et Digestive, and [2]Département d'Information Médicale, Centre Hospitalier Universitaire de Rennes, Université de Rennes 1, Rennes, France

Abstract

Objective: To evaluate the incidence, the impact on survival and the predictive factors of bile leakage (BL) in a recent large monocentric series of liver resections performed in a referral tertiary care centre.

Background: Previous reports dealing with bile leakage (BL) after liver resection are rare and have displayed conflicting results regarding incidence, impact on follow-up and predictive factors.

Methods: A retrospective review of the records of 912 patients who underwent a total of 1001 consecutive liver resections without biliary reconstruction, performed between January 2005 and May 2011. BL was defined by the presence of bile in the abdominal drains, a radiologically or surgically drained bilioma or biliary peritonitis. BL severity was established according to the Clavien–Dindo classification. Fifty-eight pre-, per- and post-resection variables were analysed and the independent BL predictive factors were identified using logistic regression.

Results: The incidence of BL was 8%. Clavien–Dindo I-II, IIIa, IIIb or IV rates were 29%, 35%, 32.5% and 2.5%, respectively. BL did not increase in-hospital mortality (2.5% versus 2.9%, $P = 1.0$), but doubled the median duration of hospital stay (16 versus 9 days, $P < 0.001$) and increased 1-year mortality (11% versus 5%, $P = 0.03$). Multivariate analysis identified that pre-operative bevacizumab [odds ratio (OR) = 2.9, confidence interval (CI) 95% = 1.58–5.41] $P = 0.001$], a major hepatectomy [OR = 2.6 (CI 95% = 1.48–4.76) $P = 0.001$], a two-stage hepatectomy [OR = 2.5 (CI 95% = 1.17–5.52) $P = 0.018$], the selective clamping technique [OR = 2.6 (CI 95% = 1.03–6.78) $P = 0.042$], R1 or R2 resection [OR = 2.6 (CI 95% = 1.52–4.64) $P = 0.001$] and the absence of a methylene blue test [OR = 2.6 (IC 95% = 1.43–4.65) $P = 0.002$] were independent risk factors of BL.

Conclusion: BL remains frequent after liver resection. It has a dramatic impact on patient survival and care costs. Its incidence could be reduced by avoiding the pre-operative use of bevacizumab, avoiding selective clamping and performing a blue dye test in all resections.

Received 14 June 2012; accepted 7 August 2012

Correspondence

Karim Boudjema, Service de Chirurgie Hépatobiliaire et Digestive, Centre Hospitalier Universitaire de Rennes, Université de Rennes 1, France. Tel: 00 33 2 99 28 98 41; Fax: 00 33 2 99 28 41 29; E-mail: karim.boudjema@chu-rennes.fr

Introduction

In the last decade, thanks to advances in surgical and peri-operative management, liver surgery has made considerable progress underpinned by the reduction in peri-operative morbidity and mortality rates which are now below 45 % and 5%, respectively, in most series.[1,2]

Among the complications of hepatic resection, bile leakage (BL) remains a serious problem. It promotes sepsis,[3] prolongs hospitalization and may increase the cost of care. Recent series of hepatectomies without biliary anastomosis reported a BL incidence of between 3.6% and 10%.[4–8]

In recent years, the indications for resection of colorectal cancer liver metastases (CRLM) have increased. The requirements for

*A. Guillaud and C. Pery have participated equally in the analysis of the data and preparation of the manuscript.

This manuscript was presented at the 10th World IHPBA Congress, Paris, 1–5 July 2012.

radical resection consist of larger and more complex resections, almost always including chemotherapy whose impact on post-hepatectomy morbidity has been demonstrated.[9] The incidence of BL remains unclear in these patients while it delays the initiation of adjuvant therapy and may therefore alter the oncological outcome, although this has not yet been proven.

The aim of this study was to analyse the impact of BL on survival and identify the risk factors associated with BL in the modern age of liver resection in a referral tertiary care centre. Special attention was paid to CRLM.

Patients and methods

A retrospective analysis of patients undergoing partial hepatectomies without biliary anastomosis between January 2005 and May 2011 at the Department of Hepatobiliary and Digestive Surgery at Rennes University Hospital was performed. Local institutional review board approval was obtained.

BL assessment

BL was assessed in three different clinical situations: (i) the presence of bile in the abdominal drains when present; (ii) percutaneous or surgical drainage of a biloma, i.e. collection adjacent to the liver parenchymal cut surface as diagnosed by ultrasound or CT scan and bringing back bile after percutaneous drainage (PD); and (iii) biliary ascites or peritonitis found at laparotomy. BL were classified according to the International Study Group of Liver Surgery (ISGLS).[10] The severity of BL was classified according to the Clavien–Dindo classification.[11]

Surgical procedures

The surgical approach was almost always a laparotomy with a J-shaped right subcostal incision. An ultrasound was always performed per-operatively. Continuous or intermittent pedicle clamping (Pringle manoeuvre) or selective clamping of the pedicles for the segment to be resected were mostly performed. Portal and suprahepatic pedicles were cut transparenchymally except when the tumour had a close relationship with the origin of the right or left portal pedicles. In this situation, intra glissonian dissection was first performed for immediate section of the artery and portal vein. With very few exceptions, a parenchymal transection was performed using an ultrasonic dissector. Vessels or bile ducts encountered during the transection were coagulated, clipped or ligated according to their size. Electrocautery or argon beamers were used for additional raw surface haemostasis when necessary. Topical haemostatic agents such as fibrinogen-coated collagen patches or fibrin glues were rarely applied to the parenchymal cut surface. An intra-operative methylene blue test was commonly performed through a trancystic tube (C-tube) in order to detect BL. The C-tube was left in position and externalized through the skin. It was clamped on the fifth post-operative day in the absence of BL and removed after 4 to 6 weeks in the outpatient clinic. Cholangiography with distal clamping was performed after surgery in case of doubt on the integrity of the biliary tract of the liver remnant.

Two closed-suction drains (pressure −700 to −950 mbar) were placed in the resection space and removed on the fifth post-operative day when drainage was minimal, serous and not bile stained. Outpatient monitoring with CT was performed at 30 days.

Definitions

Chemotherapy was considered recent if it was administered during the year prior to a hepatectomy. A period of 3 weeks and 6 to 8 weeks was mandatory between surgery and non-targeted or targeted chemotherapy, respectively.

Post-operative liver dysfunction became a failure when the '50-50 criteria' were met (serum bilirubin level above 50 µmol/l and prothrombin time less than 50% on day 5 after surgery).[12]

The nomenclature of segments and types of hepatectomies performed followed 'The Brisbane 2000 Terminology'.[13] In this setting, a major hepatectomy was defined as resection of at least three liver segments and a minor resection was defined as resection of fewer than three segments, including a wedge resection.

Data collection and statistical analysis

Data collection was carried out to meet the main objective of the predictive analysis of BL. It consisted of 58 pre-operative, intra-operative or post-operative parameters.

Data were described by means and standard deviations for quantitative variables and by absolute and relative frequencies for qualitative variables. Median and range were used to describe the time data. First, the characteristics of both groups defined by the presence or the absence of post-operative BL were compared. Wilcoxon's rank-sum test was used to compare quantitative parameters and Fisher's exact test to compare qualitative parameters. Subsequently, all variables univariately significantly associated with the presence of BL with $P < 0.2$ were presented stepwise to a multiple logistic regression model to assess their independent link with BL status. Significant risk factors were selected with a forward strategy using likelihood ratio statistics, with $P = 0.05$ on the criterion level of selection. First, the selection was separately performed by block according to the three groups of parameters (pre-, intra- and post-operative factors). The final selection of each block-selected variable was performed a second time to complete the multivariate analysis. Statistical analyses were performed with SPSS Statistics 17.0 software for Windows (SPSS Inc., Chicago, IL, USA).

Results

The analysis included 1001 consecutive resections performed in 912 patients (68.6% men and 31.4% women). Two, three, four or five successive resections were performed in 70, 6, 1 and 1 patients,

Table 1 Patient characteristics

Patient characteristics	
Age (years) (median)	64 [16;90]
Age ≥75 *n* (%)	152 (15.2)
Gender *n* (%)	
Female	318 (31.8)
Male	683 (68.2)
BMI (kg/m^2) (median)	25 [14;57]
Pre-operative cirrhosis *n* (%)	120 (12)
Child–Pugh A	120 (11.5)
Child–Pugh B	2 (0.2)

BMI, body mass index.

Table 2 Indications for hepatectomies

Indication for hepatectomies	*n* (%)
Metastatic liver tumour	504 (50.3)
Colorectal metastasis	428 (42.7)
Other liver metastasis	76 (7.6)
Primary liver tumours	497 (49.7)
Hepatocellular carcinoma	276 (27.6)
Cholangiocarcinoma	68 (6.8)
Other malignancies	31 (3.1)
Benign liver lesion	122 (12.2)

Table 3 Pre-operative treatment for metastatic tumours

Pre-operative treatment for metastatic tumours (*n* = 504)	
Chemotherapy	430 (85.3%)
Long-standing chemotherapy	64 (12.7%)
Recent chemotherapy	366 (72.6%)
Bevacizumab	93 (18.4%)
Cetuximab	48 (9.5%)

respectively. Patient characteristics and an indication for hepatectomies are summarized in Tables 1 and 2.

During the study period, 62 hepatectomies were performed in 38 patients in a two-stage strategy. The indication for this procedure was metastatic colorectal cancer except in two patients who had two hepatectomies for multiple bilobar hepatocellular adenomas and metastases of a gastrointestinal stromal tumour, respectively. In 17 out of 36 patients, a colorectal resection was combined with a first-stage hepatectomy (Table 3).

Incidence and characteristics of bile leakage

The incidence of BL was 8% (80/1001). The results are presented in Table 4. A median of 157 hepatectomies (range: 54–175) were performed yearly and the rate of BL was not different vis-à-vis the year of liver resection ($P = 0.63$) (Fig. 1).

The classification and severity of BL are reported in Table 5.

Table 4 Characteristics of bile leakage

Bile leakage	80/1001 (8%)
Median time between operation and BL	8.5 days [1;90]
Diagnosis	
• Bile into the abdominal drain	37/80 (46%)
• Biloma	42/80 (53%)
Clinical presentation:	
Fever	27/42
Abdominal pain	4/42
Both fever and abdominal pain	7/42
Incidentally	4/42
• Biliary peritonitis	1/80 (<1%)

BL, bile leakage.

BL healed with a median duration of 26 days (range: 1–153). In the group of BL diagnosed as the presence of bile in the surgical drain, 23 out of 37 had spontaneous healing after a median period of 14 days (range, range: 1–73). In this group, an endoscopic procedure and percutaneous drainage were necessary for 11 out of 37 and 3 out of 37 resections, respectively. The median duration of biloma healing after percutaneous drainage was 31 days (range: 3–150).

For patients who had a hepatectomy without BL, the median overall duration of hospitalization was 9 days (range: 1–113). It was longer in BL patients [16 days, (range: 9, 91) ($P < 0.001$)]. For non-BL and BL patients, hospital mortality rates were 2.9% and 2.5%, respectively (NS). As compared with non-BL patients, the overall 1-year survival rate was significantly lower in BL patients (89% versus 94.5%, $P = 0.035$).

The overall morbidity rate was 41.3% (413/1001). Various post-operative complications are reported in Table 6. In the BL group, 40% of the patients had at least one associated complication.

Predictive factors for bile leakage

The factors associated with bile leak on univariate analysis are shown in Table 7.

Among the 26 out of 62 two-stage hepatectomies which completed the surgical procedure with curative intent, the median time between the first and second stages was 3.2 months (range: 1.8–11.8). BL occurred in 9 out of 26 two-stage hepatectomies, 4 out of 26 after the first stage and 5 out of 26 after the second stage.

Among the 652 anatomical resections, 227 were right hepatectomies and 24 were left hemi-hepatectomies. The Hanging manoeuvre was performed in 93 out of 251 patients who underwent a right or left hepatectomy.

The BL rate was not different depending on whether or not this manoeuvre was used to cut the liver parenchyma ($P = 0.173$).

The results of the multivariate analysis are reported in Table 8.

Discussion

The aim of this study was focused on the incidence and predictive factors of BL after hepatic resection without biliary anastomosis.

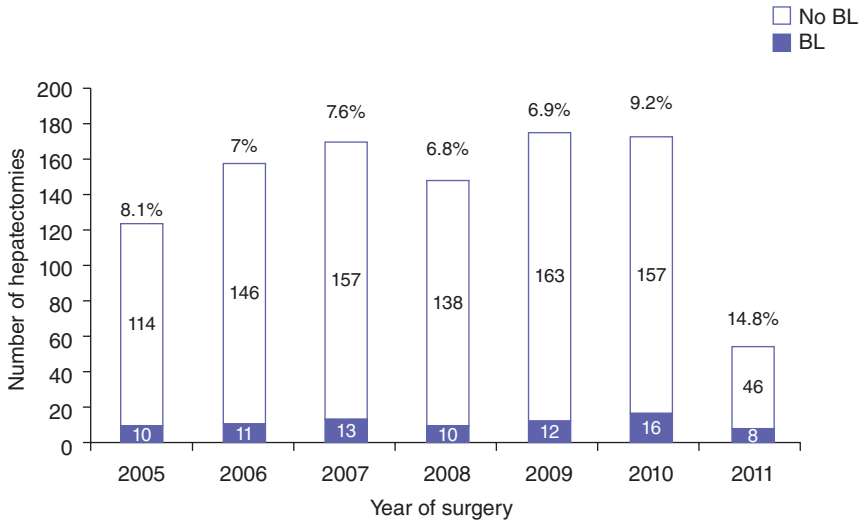

Figure 1 Incidence of bile leakage related to the year of surgery

Table 5 Severity of bile leakage

Classification	*n* (%)
Clavien-Dindo	
I	6 (7.5)
II	17 (21.2)
IIIa	28 (35)
IIIb	26 (32.5)
Iva	2 (2.5)
IVb	0 (0)
V	1 (1.3)
ISGLS	
A	6 (7.5)
B	62 (77.5)
C	12 (15)

ISGLS, International Study Group of Liver Surgery.

Table 6 Overall post-operative complications

	n (%)	Without BL (*n* = 921)	With BL (*n* = 80)	*P*
Overall morbidity	413 (41.3)	-	-	-
Bile Leakage	80 (8)	-	-	-
Other type of complication	333 (33.3)	300	33	0.137
Hepatic failure	29 (2.9)	24	5	0.074
Intra-abdominal bleeding	37 (3.7)	35	2	0.762
Intra-abdominal abscess	46 (4.6)	41	5	0.406
Abdominal wall abscess	9 (0.9)	8	1	0.529
Gastrointestinal leakage	11 (1.1)	10	1	0.6
Ascites	41 (4.1)	39	2	0.766
Pulmonary complication	65 (6.5)	56	9	0.092
Urinary complication	28 (2.8)	25	3	0.484
Thrombo-embolic complication	15 (1.5)	8	7	<10-3
Infectious complication	52 (5.2)	47	5	0.830

BL, bile leakage.

It covered a recent and large population of operated patients, at a time when liver surgery has been enriched by sophisticated techniques such as, two-stage surgery, repeat hepatectomy and involving chemotherapy whose hepato-toxic effects have been demonstrated.[14] This study has shown that BL is still common, lengthens the duration of hospitalization, increases morbidity and is associated with a reduced 1-year survival.

The complexity of strategies, i.e. two-stage hepatectomies and major resection, R1 or R2 resection, and the use of bevacizumab in patients with colorectal liver metastasis, were independent risk factors for developing a bile leak. The use of the methylene blue test was shown to be effective in reducing the incidence of BL; however, this finding should be tempered by the fact that patients who had a second resection may not have had a blue test at the time of the second set.

The present study is the first to show a reduction in patient survival when BL occurs. This could be as a result of the fact that CRLM were in high proportion and that BL could delay the initiation of adjuvant therapy and therefore worsen the prognosis. Another study is being performed to confirm this supposition.

Half of the hepatectomies performed during the study period were indicated to resect metastatic disease, the majority of which were from colorectal cancer. Peri-operative chemotherapy strategies have become frequent in the treatment of CRLM. Pre-operative chemotherapy with bevacizumab has never been shown to increase overall morbidity.[15–18] In the present study, the BL rate was significantly increased when patients received bevacizumab pre-operatively. Although we cannot support this statement with evidence, we suggest that the antiangiogenic effect of bevacizumab could have delayed the healing of minor bile leakage.

Table 7 Predictive factors of bile leakage: univariate analysis

Factor	Without BL (*n* = 921)	With BL (*n* = 80)	*P*
Pre-operative factors			
Age >75 years	144	8	0.197
Recent chemotherapy	319	47	<10-3
Associated biotherapy	117	20	<10-3
Bevacizumab	74	19	<10-3
Portal vein embolization	99	13	0.139
Intra-operative factors			
Laparotomy	879	80	0.043
Duration of surgery (min)(min-max)	155 (30–620)	202 (90–480)	<10-3
Two-stage hepatectomy	49	13	0.001
Repeat hepatectomy	159	24	0.016
Blood transfusion	193	31	<10-3
Major hepatectomy	481	58	<10-3
Non-anatomical hepatectomy	225	16	0.13
Right hepatectomy+segment 1	15	4	0.058
Extended right hepatectomy+ segment 1	7	4	0.008
Left hepatectomy+segment 1	19	5	0.036
Segment 3	12	3	0.111
Segment 5	12	3	0.111
Segment 6	18	4	0.092
Right posterior sectionectomy	53	1	0.117
Wedge of segment 1	14	3	0.148
Portal vein ligation	35	7	0.072
Intra-operative radiofrequency	40	7	0.092
Vascular-associated resection	16	4	0.068
Venous resection	14	4	0.049
Portal vein resection	5	3	0.021
Selective clamping	87	15	0.042
Pedicular clamping (min-max)	26 (1–110)	29.5 (3–91)	0.091
Vena caval clamping (min-max)	25 (1–85)	16 (2–37)	0.056
No methylene blue test	470	50	0.061
Raw cut treatment	234	30	0.024
Fibrin glue	78	15	0.007
Surgical drain	823	77	0.052
Anatomopathological factors			
Metastasis	457	47	0.13
Resection R1 or R2	120	25	<10-3

BL, bile leakage.

Table 8 Predictive factors of bile leakage: multivariate analysis

Factor	OR	95% CI
Use of bevacizumab	2.92	1.58–5.41
Major resection	2.65	1.48–4.76
R1 or R2 resection	2.65	1.52–4.64
Selective clamping	2.65	1.03–6.78
Absence of the methylene blue test	2.57	1.43–4.65
Two-stage surgery	2.55	1.17–5.52

OR, odds ratio; CI, confidence interval.

As far as a two-stage hepatectomy for metastases is concerned, the Princeps study by Adam *et al.*[19] did not report BL among the post-operative complications. Since then, only four other studies reporting the results of two-stage hepatectomies have considered BL[20–23] and none of them reported BL after the first stage. However, BL after the second stage ranged from 2.6% to 21%. As compared with these data, although the incidence of leakage after the second hepatectomy was similar, the current rate of BL after the first hepatectomy was higher than previously reported. This may be because of the fact that our strategy was to achieve radical resection of liver remnant metastases rather than use local destruction methods such as radio frequency ablation or cryotherapy. This choice relies on the fact that, as compared with thermal ablation, radical resection has been shown to reduce recurrence and improve survival.[24]

Among the studies on the risk factors of BL after a hepatectomy, only a single retrospective study reported, in univariate analysis, an increase of BL in R1 and R2 surgery.[25] This may be related to injuries to major Glissonian sheaths when attempting resection of adherent or invasive lesions. Another explanation would be persistent tumour tissue at the cut surface, forming a brittle zone with biliary alterations which is the source of leaks.

The methylene blue test was associated with a reduced incidence of BL. This was in line with the results of Lam *et al.*[5] who analysed BL in a series of 616 consecutive liver resections for malignant or benign tumours. In this study, the methylene blue test was performed on 304 patients (49%) and was associated with a significant reduction in BL incidence. However, the value of intra-operative tests to prevent BL is still debated.[26,27] Indeed, it has been argued that dye tests do not check for leaks from excluded segments and that the injection of dye through the cystic duct could be responsible for barotrauma which can break the fragile ligatures and ultimately create a leak or be the cause of reflux cholangitis.[28] Moreover, a dye test makes it necessary to perform a cholecystectomy which is not always necessary in minor or wedge liver resections, may not be feasible during iterative liver resection and has a specific morbidity.[29]

Conclusion

BL is still common after a hepatectomy and it prolongs hospitalization and alters survival. The advent of biotherapies and the complexity of the strategies are risk factors.

The methylene blue test could be a good way to reduce the incidence of BL.

Bevacizumab is the only biotherapy that has obtained marketing authorization for the first-line treatment of liver metastases of colorectal cancer. In our hands, its administration was associated with an increased risk of BL, an observation that raises the question of the time interval between the end of administration of bevacizumab and liver resection.

Conflicts of interest

The authors of this manuscript have no conflicts of interest to disclose as described by the journal. The manuscript is not funded in part or full by any entity.

References

1. Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S *et al*. (2002) Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg* 236:397–406; discussion 06–7.
2. Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK *et al*. (2004) Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. *Ann Surg* 240:698–708; discussion 08–10.
3. Andersson R, Tranberg KG, Bengmark S. (1990) Roles of bile and bacteria in biliary peritonitis. *Br J Surg* 77:36–39.
4. Yamashita Y, Hamatsu T, Rikimaru T, Tanaka S, Shirabe K, Shimada M *et al*. (2001) Bile leakage after hepatic resection. *Ann Surg* 233:45–50.
5. Lam CM, Lo CM, Liu CL, Fan ST. (2001) Biliary complications during liver resection. *World J Surg* 25:1273–1276.
6. Capussotti L, Ferrero A, Vigano L, Sgotto E, Muratore A, Polastri R. (2006) Bile leakage and liver resection: where is the risk? *Arch Surg* 141:690–694; discussion 95.
7. Ishii H, Ochiai T, Murayama Y, Komatsu S, Shiozaki A, Kuriu Y *et al*. (2011) Risk factors and management of postoperative bile leakage after hepatectomy without bilioenteric anastomosis. *Dig Surg* 28:198–204.
8. Yoshioka R, Saiura A, Koga R, Seki M, Kishi Y, Yamamoto J. (2011) Predictive factors for bile leakage after hepatectomy: analysis of 505 consecutive patients. *World J Surg* 35:1898–1903.
9. Karoui M, Penna C, Amin-Hashem M, Mitry E, Benoist S, Franc B *et al*. (2006) Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. *Ann Surg* 243:1–7.
10. Koch M, Garden J, Padbury R, Rahbari N, Adam R *et al*. (2011) Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. *Surgery* 149:680–688.
11. Dindo D, Demartines N, Clavien PA. (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 240:205–213.
12. Balzan S, Belghiti J, Farges O, Ogata S, Sauvanet A, Delefosse D *et al*. (2005) The '50-50 criteria' on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. *Ann Surg* 242:824–828; discussion 28–9.
13. Strasberg SM. (2005) Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. *J Hepatobiliary Pancreat Surg* 12:351–355.
14. Laurent C, Sa Cunha A, Couderc P, Rullier E, Saric J. (2003) Influence of postoperative morbidity on long-term survival following liver resection for colorectal metastases. *Br J Surg* 90:1131–1136.
15. D'Angelica M, Kornprat P, Gonen M, Chung KY, Jarnagin WR, DeMatteo RP *et al*. (2007) Lack of evidence for increased operative morbidity after hepatectomy with perioperative use of bevacizumab: a matched case-control study. *Ann Surg Oncol* 14:759–765.
16. Kesmodel SB, Ellis LM, Lin E, Chang GJ, Abdalla EK, Kopetz S *et al*. (2008) Preoperative bevacizumab does not significantly increase postoperative complication rates in patients undergoing hepatic surgery for colorectal cancer liver metastases. *J Clin Oncol* 26:5254–5260.
17. Reddy SK, Morse MA, Hurwitz HI, Bendell JC, Gan TJ, Hill SE *et al*. (2008) Addition of bevacizumab to irinotecan- and oxaliplatin-based preoperative chemotherapy regimens does not increase morbidity after resection of colorectal liver metastases. *J Am Coll Surg* 206:96–106.
18. Chaudhury P, Hassanain M, Bouganim N, Salman A, Kavan P, Metrakos P. (2010) Perioperative chemotherapy with bevacizumab and liver resection for colorectal cancer liver metastasis. *HPB* 12:37–42.
19. Adam R, Laurent A, Azoulay D, Castaing D, Bismuth H. (2000) Two-stage hepatectomy: a planned strategy to treat irresectable liver tumors. *Ann Surg* 232:777–785.
20. Wicherts DA, Miller R, de Haas RJ, Bitsakou G, Vibert E, Veilhan LA *et al*. (2008) Long-term results of two-stage hepatectomy for irresectable colorectal cancer liver metastases. *Ann Surg* 248:994–1005.
21. Homayounfar K, Liersch T, Schuetze G, Niessner M, Goralczyk A, Meller J *et al*. (2009) Two-stage hepatectomy (R0) with portal vein ligation – towards curing patients with extended bilobular colorectal liver metastases. *Int J Colorectal Dis* 24:409–418.
22. Karoui M, Vigano L, Goyer P, Ferrero A, Luciani A, Aglietta M *et al*. (2010) Combined first-stage hepatectomy and colorectal resection in a two-stage hepatectomy strategy for bilobar synchronous liver metastases. *Br J Surg* 97:1354–1362.
23. Tsim N, Healey AJ, Frampton AE, Habib NA, Bansi DS, Wasan H *et al*. (2011) Two-stage resection for bilobar colorectal liver metastases: R0 resection is the key. *Ann Surg Oncol* 18:1939–1946.
24. Abdalla EK, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio KR *et al*. (2004) Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg* 239:818–825; discussion 25–27.
25. Erdogan D, Busch OR, van Delden OM, Rauws EA, Gouma DJ, van Gulik TM. (2008) Incidence and management of bile leakage after partial liver resection. *Dig Surg* 25:60–66.
26. Ijichi M, Takayama T, Toyoda H, Sano K, Kubota K, Makuuchi M. (2000) Randomized trial of the usefulness of a bile leakage test during hepatic resection. *Arch Surg* 135:1395–1400.
27. Li J, Malago M, Sotiropoulos GC, Lang H, Schaffer R, Paul A *et al*. (2009) Intraoperative application of 'white test' to reduce postoperative bile leak after major liver resection: results of a prospective cohort study in 137 patients. *Langenbecks Arch Surg* 394:1019–1024.
28. Yoshimoto H, Ikeda S, Tanaka M, Matsumoto S. (1989) Relationship of biliary pressure to cholangiovenous reflux during endoscopic retrograde balloon catheter cholangiography. *Dig Dis Sci* 34:16–20.
29. Kovalcik PJ, Burrell MJ, Old WL, Jr. (1983) Cholecystectomy concomitant with other intra-abdominal operations. Assessment of risk. *Arch Surg* 118:1059–1062.